Tetrahedron Letters, Vol.22, No.18, pp 1657 - 1660, 1981
Printed in Great Britain

0040-4039/81/181657-04$02.00/0

STEREOSELECTIVE SYN EPOXIDATION OF THE DIHYDRODIOLS OF DIBENZ[a,h] ANTHRACENE AND 7-METHYLBENZ[a] ANTHRACENE

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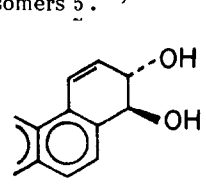
ABSTRACT: Epoxidation of the bay region dihydrodiols of the title hydrocarbons affords stereoselectively the corresponding syn diol epoxides rather than the anticipated isomeric anti diol epoxides, indicative of a dominant cis-directing effect of the benzylic vs the allylic axial hydroxyl groups.

Carcinogenic polycyclic hydrocarbons have recently been shown to undergo metabolic activation to mutagenic trans dihydrodiols which undergo further enzymatic oxidation to reactive diol epoxide derivatives[1] which bind covalently to nucleic acids[1c] and induce tumor formation.[2] Dihydrodiols, sterically free to adopt the pseudoequatorial conformation (e.g. 1) undergo stereospecific epoxidation with m-chloroperbenzoic acid to afford the anti isomeric diol epoxides 3,[3] while bay region dihydrodiols sterically constrained to exist in the pseudodiaxial conformation 2 [4,5] are reported to afford stereoselectively the corresponding anti isomeric diol epoxides 4 accompanied by lesser amounts of the related syn isomers 5.[1a,6-10]



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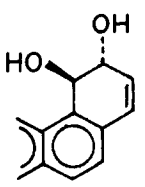

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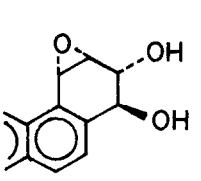

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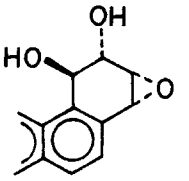

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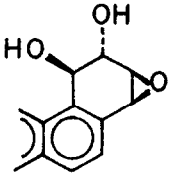

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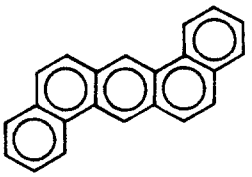
We recently described the synthesis of the isomeric diol epoxides derived from the dihydrodiols of the carcinogenic hydrocarbons dibenz[a,h] anthracene (6)[9] and 7-methylbenz[a] anthracene (7).[10] Epoxidation of the bay region dihydrodiols afforded a mixture of isomeric diol epoxides,[11] and it was tentatively assumed on the basis of precedent that the anti isomers were predominant. We now report results of a hydrolysis study which leads to the opposite stereochemical assignments, the first examples of syn-stereoselective epoxidation of arene dihydrodiols.



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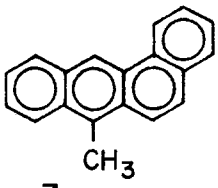

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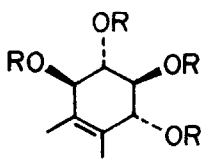
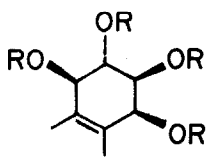
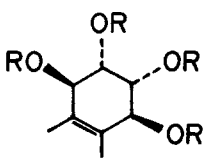
Epoxidation[12] of the 1,2-dihydrodiol of 6 afforded a 1:3 mixture of the corresponding anti and syn diol epoxides, 4 and 5, separated by HPLC on a Zorbax Sil column.[13] Hydrolysis of the syn isomer afforded the pair of tetraols arising from cis and trans addition of water to the epoxide ring.[14,15] The tetraols were converted to their tetraacetate derivatives (8a,b) with acetic anhydride-pyridine, separated by HPLC (which showed a 4:1 ratio of trans and cis addition products),[12] and identified by proton NMR analysis. Similar treatment of the anti form gave only a single tetraacetate (8c) (arising from trans addition), the NMR spectrum of which matched closely that of the tetraacetate formed from the anti diolepoxide of the 3,4-dihydrodiol of 6.[9,11] Epoxidation of the 1,2-dihydrodiol of 7 gave a mixture of the anti and syn diol epoxides, 4 and 5 in a 1:9 ratio. Hydrolysis of the predominant syn isomer followed by acetylation furnished the corresponding trans and cis tetraacetates (8a' and 8b') in ~ 2:1 ratio. Hydrolysis of the anti isomer was not investigated due to the insufficient quantity of the substrate available.



8a,a'



8b,b'



8c

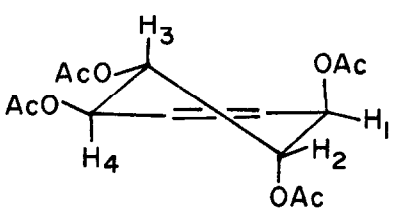
The stereochemical assignments of the tetraacetates are based on their proton NMR spectra (Table 1). Due to steric crowding in the bay regions, the 1,2-diacetoxy groups are forced to adopt an essentially diaxial conformation.[4,5] The observed $J_{1,2}$ = 4.0 Hz is consistent with values reported for the analogous bay region protons of the related tetraacetates of benzo[a]pyrene[16] and benzo[e]pyrene.[17] The relative orientation of the adjacent ring protons may be deduced from the magnitude of the coupling constants. The trans-cis-trans relationship between the adjacent methine protons of 8c in a normal half-chair structure (9) is supported by the observed values of $J_{2,3}$ = 2.7 and $J_{3,4}$ = 8.7 Hz which are consistent with the relative magnitude of the dihedral angles between H_2 and H_3 (equatorial-axial) and between H_3

and H_4 (diaxial).[18] The assignment of 8c is further supported by its identity with the tetraacetate from hydrolysis of the isomeric anti diol epoxide with the epoxide ring in the 1,2-position.[9,11] It is also consistent with the general finding that hydrolysis of anti diol epoxides proceeds with high stereoselectivity).

Table I. Proton NMR Spectra of Tetraacetates[a]

Compd	Chemical shifts (δ)					Coupling constants (Hz)		
	Acetate methyl	H_1	H_2	H_3	H_4	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$
Dibenz[a,h] anthracene derivatives								
8a	2.09,2.10,2.13,2.26	6.99	5.67	5.46	6.52	4.0	7.4	7.4
8b	2.16,2.17,2.24,2.25	7.04	6.02	5.45	6.49	4.0	10.0	3.5
8c	2.13,2.24,2.25,2.30	6.89	5.78	5.71	6.64	4.0	2.7	8.7
7-Methylbenz[a] anthracene derivatives								
8a'	2.11,2.15,2.19,2.28	6.98	5.66	5.45	6.49	4.3	7.7	7.3
8b'	2.07,2.10,2.18,2.19	7.0	6.0	5.4	6.48	4.0	9.6	3.6

[a]Taken in $CDCl_3$ at 270 MHz with tetramethylsilane as internal standard.



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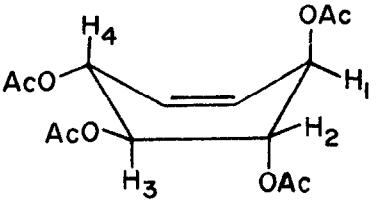

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The assignment of 8a is inconsistent with a half-chair conformation for which diequatorial coupling ≃ 2-4 Hz is expected, but is in good agreement with the boat conformation 10. Preferential existence of 8a as the boat structure appears to be a consequence of the serious 1,3-steric interactions between the acetoxy groups of the half-chair conformation. Similarly the assignments of 8a' and 8b,b' are entirely consistent only with the respective boat conformers.

On the basis of these results, we conclude that the previous assignments[9,10] of the major and minor diol epoxides produced on epoxidation of the trans-1,2-dihydrodiols of 6 and 7 should be reversed. This unexpected syn-stereoselective epoxidation is interpreted as due to exertion of steric control over epoxidation by the axial benzylic hydroxyl groups, whereas the equatorial allylic hydroxyl groups tend to control the stereochemistry in other cases. These results underline the need for caution in assigning the stereochemistry of synthetic diol epoxides.

REFERENCES AND FOOTNOTES

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2. For leading references cf. T. J. Slaga, G. L. Gleason, G. Mills, L. Ewald, P. P. Fu, H. M. Lee, and R. G. Harvey, Cancer Res. 40, 1981 (1980).
3. The anti isomers bear the epoxide oxygen atom and the benzylic hydroxyl group on the oposite faces of the molecule, while the syn isomers have these groups on the same face. The anti isomers are implicated as the principal carcinogenic metabolites formed in cells.[1,2]
4. Bay region dihydrodiols such as trans-1,2-dihydroxy-1,2-dihydrobenz[a]anthracene, -dibenz[a,h]-anthracene, and -7-methylbenz[a]anthracene are shown by NMR and X-ray crystallographic evidence to exist exclusively in the diaxial conformation both in solution and in the crystal lattice.[5]
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9. H. M. Lee and R. G. Harvey, J. Org. Chem., 45, 588 (1980).
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11. Analogous epoxidation of the less sterically restricted trans-3,4-dihydrodiols of 6 and 7 furnished exclusively the corresponding bay region anti diol epoxides 3.
12. Epoxidation was conducted with a tenfold excess of m-chloroperbenzoic acid in THF at ambient temperature for 1 hr.[9]
13. HPLC was carried out on a Dupont Zorbax Sil (6.2 mm x 25 cm) column. Diol epoxides were eluted with 1% methanol in 40% THF-hexane (4 ml/min) at room temperature. Tetraacetates were eluted with 30% THF-hexane (3 ml/min).
14. The diol epoxides were treated with dil. HCl (pH 4) in THF and water (1:1) at 42°C for 24 hr, and the resulting tetraols isolated by conventional procedures.
15. R. G. Harvey and P. P. Fu in ref. 1a, Vol. 1, Chap. 6, p. 133.
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18. The observed coupling constants in this series are consistent with those reported for the structurally related conduritols by Abraham et al., J. Chem. Soc., 6268 (1965).

(Received in USA 23 September 1980)